ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2015, 51, 8939

Received 27th March 2015,
Accepted 23rd April 2015

DOI: 10.1039/c5cc02552d

www.rsc.org/chemcomm

Stereoselective synthesis of glycosides using (salen)Co catalysts as promoters†

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The use of (salen)Co catalysts as a new class of bench-stable stereoselective glycosylation promoters of trichloroacetimidate glycosyl donors at room temperature is described. The conditions are practical and do not require the use of molecular sieves with products being isolated in good to high yields.

Access to structurally defined oligosaccharides in sufficient amounts to be used as probes for biological research, still represents a significant challenge due to the structural complexity of carbohydrates. The stereoselective coupling of glycosides is often considered the main bottleneck towards this goal and despite significant efforts devoted to the development of efficient glycosylation strategies, there is still a need for robust and practical methods to achieve this crucial step.[1]

Transition metal catalysis applied to oligosaccharide synthesis offers great promise at achieving high yields and anomeric selectivities by the careful choice of the metal and ligands attached to the metal centre.[2]

As part of our ongoing interest in developing catalytic methods for the stereoselective synthesis of glycosides,[3] we decided to focus our attention on the use of transition metal complexes in glycosylation reactions. Chiral (salen)Co(III) complexes have been developed by the Jacobsen team for the elegant preparation of both enantiopure terminal epoxides and highly enantioenriched 1,2-diols.[4] The (salen)Co catalysed asymmetric epoxide ring-opening reactions proceed *via* cooperative bimetallic mechanisms, whereby both the epoxide electrophile and nucleophile are activated by separate (salen)Co complexes in the rate-limiting ring opening step.[5] We envisioned that these chiral Co complexes would be applicable to glycosylation reactions where an electrophile glycosyl donor reacts with the corresponding nucleophile glycoside acceptor and could provide a more efficient glycosylation methodology than currently available processes.

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† Electronic supplementary information (ESI) available: Experimental procedures, data and NMR spectra. See DOI: 10.1039/c5cc02552d

Anomeric trichloroacetimidates are among the most effective and commonly used glycosyl donors in the chemical synthesis of oligosaccharides.[6] These type of glycosides are activated by Lewis acids such as TMSOTf,[7] boron trifluoride etherate[8] or lithium triflate,[9] ionic liquids,[3a,b,10] transition metals[11] and organocatalysts[12] among others. However, many of the strategies developed thus far require the use of strict anhydrous conditions/molecular sieves and low temperatures, and suffer from additional problems associated with the stability and reactivity of the promoters.[6a] Herein we report the application of chiral oligomeric (salen)Co complexes as bench-stable stereoselective glycosylation promoters of trichloroacetimidate glycoside donors.

In our initial studies, perbenzylated glucose trichloroacetimidate **3** was employed as the model glycoside donor in reactions with glycoside acceptor **4a** (Fig. 1 and Table 1). No reaction was observed when monomeric (salen)Co complex **1a** (10 mol%) was used as the catalyst (Table 1, entry 1), however when triflate ($^{-}$OTf, **1b**) was used as the counter ion, the reaction proceeded to give the desired glycosylation product **5a**, albeit slowly (22 h), in 89% yield with no stereocontrol (entry 2). Changing the catalyst to the opposite enantiomer **1c** did not yield any significant changes in yield or

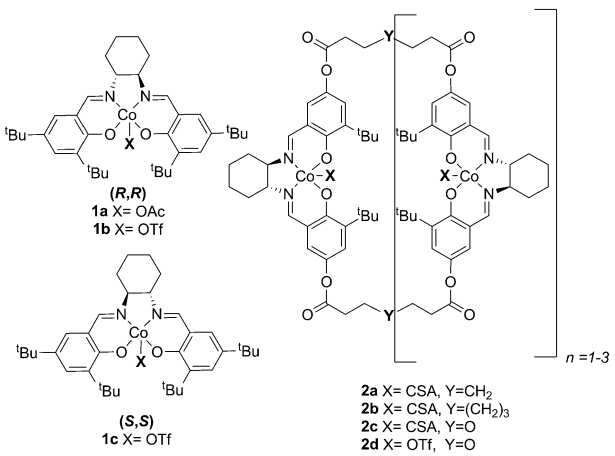
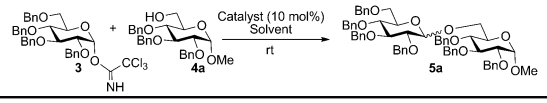


Fig. 1 (salen)Co catalysts as glycosylation promoters.

Table 1 Reaction optimization of trichloroacetimidate **3** with model acceptor **4a**



Entry	Catalyst	Solvent	T (h)	Yield (%)	$\alpha:\beta^a$
1	**1a**	CH_2Cl_2	24	n/o	n/o
2	**1b**	CH_2Cl_2	22	89	1 : 1.5
3	**1c**	CH_2Cl_2	0.5	74	1.3 : 1
4	**2a**	CH_2Cl_2	24	64	1 : 2.6
5	**2b**	CH_2Cl_2	24	n/o	n/o
6	**2c**	CH_2Cl_2	22	70	1 : 2.6
7	**2d**	CH_2Cl_2	0.5	89	1 : 2.6
8	**2d**[b]	CH_2Cl_2	1	n/o	n/o
9	**2d**[c]	CH_2Cl_2	1	70[d]	1.5 : 1
10	**2d**	THF	1	<50[e]	1 : 1
11	**2d**	Toluene	1	<50[e]	1 : 1
12	**2d**	MeCN	1	92	1 : 4
13	**2d**	Diethyl ether	1	96	2.6 : 1

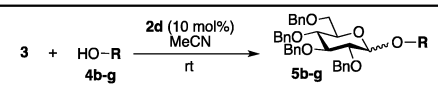
[a] Measured by ^{1}H NMR unless stated otherwise. [b] 2 mol% catalyst loading. [c] 5 mol% catalyst loading. [d] Starting material recovered. [e] Product isolated mixed with hydrolyzed starting materials. n/o = not observed.

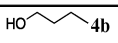
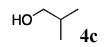
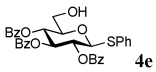
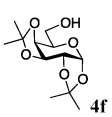
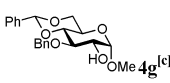
stereo-outcome of the reaction. Based on these results, we decided to move onto the cyclic, oligomeric linked C_2 symmetric (salen)Co catalysts, which have been shown to be more reactive than their monomeric counterparts and able to provide better stereocontrol in some cases.[4c,d,f] Encouragingly, reactions in the presence of 10 mol% of 1st generation oligomeric (salen)Co catalyst **2a**[4c] in dichloromethane, afforded the product in 64% yield and with a 1 : 2.6 $\alpha:\beta$ anomeric ratio after 24 h (entry 4). Extending the linker chain by two carbon units as in azelate-linked **2b**[4d] resulted in an inactive catalyst (entry 5). However, introduction of an oxygen atom in the linker while maintaining the linker length (**2c** *vs.* **2a**) yielded **5** in 70% isolated yield and in a 1 : 2.6 $\alpha:\beta$ ratio (Table 1, entry 6). It has been shown that small changes in the oligomeric catalyst structure can have a noticeable effect on the range of reactive conformations available[4d] and thus we attribute the lack of reactivity of **2b** to the added flexibility that this catalyst possesses in comparison to the other oligomeric ones tested. Remarkably, when oligomeric Co catalyst **2d**, which bears a triflate ($^-$OTf) as the counter ion instead of (1*S*)-(+)-10-camphorsulfonate (CSA), was used, the reaction proceeded faster (under 30 min.) and afforded the product in 87% yield and with similar levels of anomeric stereocontrol as observed with the other active oligomeric catalysts (Table 1, entry 7).[13] Furthermore, lowering the catalyst (**2d**) loading to 5 or 2 mol% was detrimental to the reaction yield and stereoselectivity (Table 1, entries 8 and 9). It is noteworthy that molecular sieves, which are typically used in glycosylation reactions to remove traces of water, were not needed. Next, we decided to explore solvent effects. Reactions using either THF or toluene using 10 mol% of **2d** afforded low yields and anomeric mixtures of glycosylated products (Table 1, entries 10 and 11). Stereoselectivity was improved towards the β-anomer when acetonitrile was used as the solvent, and **5a** was isolated in 92% yield as a 1 : 4 $\alpha:\beta$ ratio. On the other hand, when diethyl ether was employed, the α-product was favoured and the desired disaccharide was isolated in 96% as a 2.6 : 1 $\alpha:\beta$ mixture (Table 1, entries 12 and 13).

Having established optimal reaction conditions, we turned our attention to exploring the acceptor scope of the reaction. To that end, glycosyl donor **3** was reacted with a range of OH nucleophiles (Table 2). In all cases, reactions proceeded smoothly within 1 h. Glycosylations with aliphatic alcohols (**4b–d**) led to the expected products in high yields (78–94%) and anomeric ratios ranging from 1 : 4.9 to 1 : 5.3 $\alpha:\beta$ (Table 2, entries 1–3). Glycosyl acceptors with a primary or secondary alcohol and bearing either benzyl, benzoyl or acetal protecting groups, and either methoxy or thiophenyl as the anomeric substituent (**4e–g**) were also screened and gave isolated yields of 74–85%, with anomeric ratios that range from 1 : 4.3 to complete α-selectivity (Table 2, entries 4–6). These results highlight that oligomeric salen(Co) catalyst **2d** is tolerant of most commonly used alcohol functional groups and that the reactivity is independent of the position of the free hydroxyl on the acceptor. Furthermore, the reaction conditions are semi-orthogonal to thioglycoside chemistry (Table 2, entry 4), making this reagent suitable for chemoselective glycosylations where a trichloroacetimidate glycosyl donor can be selectively activated in the presence of a thioglycoside building block.

Encouraged by the acceptor scope of the catalyst, glycosylations with other common glycoside donors were also investigated. Reactions of perbenzylated galactose **6a** with either **4b** or **4f** led to the desired products **7** and **8** in 82% and 90% yields with good to moderate anomeric β-selectivities (Table 3, entries 1 and 2). When activated mannose **6b** was reacted with **4e** or **4f** as the nucleophiles, the corresponding disaccharides **9** and **10** were isolated in 60% and 62% yields with reasonable to moderate α-selectivity, respectively (Table 3, entries 3 and 4). Reactions involving "disarmed" donor **6c** with **4a** or **4f** were less efficient and proceeded in modest yields, albeit with complete β-stereocontrol as expected from less reactive glycosyl donors bearing a participating group at C-2[14] (Table 3, entries 5 and 6). 6-Deoxyglycosides are also an important class

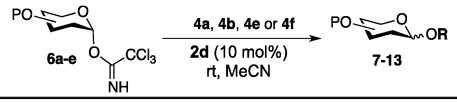
Table 2 Acceptor Scope in the glycosylation of glucosyl donor **3**[a]

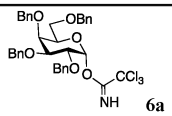
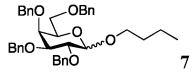
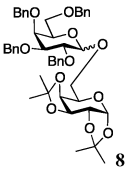
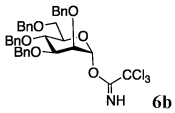
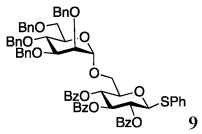
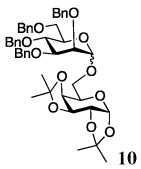
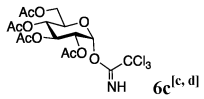
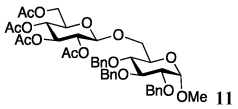
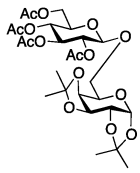
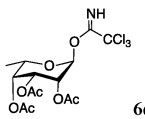
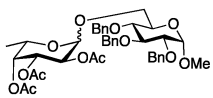


Entry	ROH	Yield (%)	$\alpha:\beta^b$
1	 **4b**	88	1 : 4.9
2	 **4c**	78	1 : 5.3
3	 **4d**	78	1 : 5.3
4	 **4e**	74	α
5	 **4f**	94	1 : 4.3
6	 **4g**[c]	85	9 : 1

[a] All reactions carried out with 1.2 equiv. **3** and 1.0 equiv. of **4b–g**. [b] From ^{1}H NMR. [c] Reaction run in CH_2Cl_2.

Table 3 Glycosyl donor scope[a]



Entry	Donor	Product	Yield (%)	$\alpha:\beta$[b]
1	 **6a**	 **7**	82	1 : 6
2	**6a**	 **8**	90	1 : 3
3	 **6b**	 **9**	60	7.2 : 1
4	**6b**	 **10**	62	4 : 1
5	 **6c**[c, d]	 **11**	50	β
6	**6c**[c]	 **12**	52	β
7	 **6d**	 **13**	83	1 : 4.9

[a] All reactions carried out with 1.2 equiv. **7** and 1.0 equiv. of **4**. [b] From ^{1}H NMR. [c] Reaction run in CH_2Cl_2. [d] 4 equiv. of **6c** were used.

of compounds often found as conjugates of natural products. Moreover, the stereoselective synthesis of this type of glycans is further complicated by the lack of oxygen substituents at C-6.[15] Coupling between fucosyl trichloroacetimidate **6d** with **4a** proceeded in good yields and the corresponding disaccharide **13** was isolated in 83% yield with a preference for the β-product (1 : 4.9 $\alpha:\beta$) (Table 3, entry 7).

In conclusion, we have described the application of oligomeric salen(Co) catalysts as a new class of stereoselective promoters in glycosylation reactions involving trichloroacetimidate glycosyl donors. The bench-stable catalyst can be easily prepared in multi-gram quantities from inexpensive and commercially available starting materials. The reactions proceed cleanly and in good to excellent yields at room temperature and without the need for molecular sieves. Furthermore, the conditions are practical, mild and applicable to different types of glycosyl donors and acceptors, tolerant of most common hydroxyl protecting groups (*e.g.* acetates, benzoates, alkyl and benzyl ethers and acetals) and semi-orthogonal to thioglycoside chemistry. The robustness of the catalyst and ease of use in often troublesome coupling reactions, makes this class of catalyst a promising synthetic tool for diastereoslective acetal chemistry.

MCG thanks the EPSRC EP/L001926/1 CAF and EP/J002542/1 (MCG, SM) for funding. ASH thanks EPSRC Bristol Chemical Synthesis CDT EP/G036764/1 and JFB thanks the Royal Society for a University Research Fellowship.

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